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Prognostic Significance of Coronary Thrombus in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes

A Subanalysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial

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Objectives The objective of this study is to investigate the incidence and clinical implications of thrombus on baseline angiography among patients presenting with non–ST-segment elevation acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI).

Background Given current advances in the pharmacological and mechanical treatment of ACS patients managed with an early invasive strategy, the incidence and prognostic importance of pre-procedural lesion thrombus is warranted.

Methods In the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial, a total of 3,627 patients with moderate- and high-risk ACS undergoing PCI had their baseline and final post-PCI angiograms analyzed by an independent angiographic core laboratory.

Results Patients with thrombus (n = 530 [15%]) compared with those without thrombus had higher rates of impaired final epicardial coronary flow (final Thrombolysis In Myocardial Infarction [TIMI] flow grade 3: 89.6% vs. 97.1%, $p < 0.0001$). Thrombus was an independent predictor of 30 day death (odds ratio [OR]: 3.16 [95% confidence interval (CI): 1.20 to 8.37], p = 0.02), and myocardial infarction (MI) at 30 days (OR: 1.62 [95% CI: 1.17 to 2.24], p = 0.003) and at 1 year (OR: 1.56 [95% CI: 1.16 to 2.08], p = 0.003). Patients with thrombus had significantly higher rates of stent thrombosis (ST) compared with patients without thrombus at 30 days (2.8% vs. 1.1%, p = 0.002) and at 1 year (3.7% vs. 1.8%, p = 0.003), and thrombus was an independent predictor of ST at both 30 days (OR: 2.61 [95% CI: 1.38 to 4.91]) and 1 year (OR: 2.98 [95% CI: 1.64 to 5.42]).

Conclusions Pre-procedural thrombus was present in 15% of moderate- and high-risk ACS patients undergoing PCI in the ACUITY trial. Baseline thrombus predicts increased ischemic complications at 30 days including a 3-fold increased risk of death as well as MI up to 1 year. Further evaluation of adjunctive pharmacotherapy is needed in this high-risk population. (J Am Coll Cardiol Intv 2011;4: 769–77) © 2011 by the American College of Cardiology Foundation

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Pre-procedural thrombus is a harbinger of procedural complications following primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (MI) (1–3). Thrombus can lead to poor outcomes by various mechanisms including distal embolization, impaired myocardial perfusion, increased myocardial necrosis and decreased left ventricular function (4,5), with subsequent reduced survival benefit at follow-up (6–8). The purpose of this study is to determine the incidence, predictors and prognosis of pre-procedural thrombus among moderate- and high-risk acute coronary syndromes (ACS) patients undergoing contemporary guideline-recommended PCI in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial (9–12).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
DES = drug-eluting stent(s)
GPI = glycoprotein IIb/IIIa inhibitor
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
RR = relative risk
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

Methods

Study population and design. The design and results of the ACUITY trial have been previously published (12,13). Briefly, 13,819 patients with moderate- and high-risk ACS were randomized in an open-label fashion to 1 of 3 antithrombotic regimens: heparin (unfractionated or enoxaparin at site discretion) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy. Patients assigned to heparin plus a GPI or bivalirudin plus a GPI were randomly assigned again in a 2-by-2 factorial design to either upstream or deferred initiation. In patients assigned to bivalirudin monotherapy, GPI administration was reserved for "bail-out" use for procedural PCI complications or suboptimal results.

Coronary angiography was required per protocol within 72 h of randomization, with subsequent triage to treatment with PCI, coronary artery bypass grafting (CABG), or medical management at the physician's discretion. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent.

Angiographic analysis. Comprehensive quantitative coronary angiography of baseline and final angiograms from 6,921 consecutive patients from the U.S. centers was performed by an independent angiographic core laboratory. All angiograms were evaluated by reviewers blinded to treatment assignment using validated quantitative methods (Medis, Leiden, the Netherlands). Complete baseline and post-procedural angiographic data were available in 3,627 patients undergoing PCI. Coronary thrombus was defined as an intraluminal filling defect or an area of contrast staining noted within the target stenosis. Thrombus burden was assessed as the total area based on the diameter and length of the observed angiographic thrombus. Abrupt closure was defined as a decrease in Thrombolysis In Myocardial Infarction (TIMI) flow to grade 0 or 1 with recurrent stenosis similar to or worse than that present before PCI. No-reflow was defined as reduced antegrade flow (TIMI flow grade <2) in the absence of occlusion at the treatment site or evidence of distal embolization. Distal embolization was defined as the migration of a filling defect to distally occlude the infarct-related vessel or 1 of its branches, or a new abrupt cutoff of the distal vessel or its branch. Other variables included baseline TIMI flow grade and myocardial blush score assessed on a scale of 0 to 3 using methods previously described (14,15). The extent of coronary artery disease (CAD) was quantified by an angiographic surrogate of disease burden (the total length in millimeters of all lesions with a >30% diameter stenosis in a major epicardial vessel), and the Duke Jeopardy Score estimating the amount of myocardium at risk on the basis of the particular location of coronary artery stenosis, in which a higher score corresponds to a greater area of jeopardized myocardium (16).

Definitions and statistical analyses. The endpoints of this analysis included: 1) composite ischemia (defined as death from any cause, MI, or unplanned revascularization for ischemia); 2) definite or probable stent thrombosis (ST) at 30 days and at 1 year; and 3) non-CABG–related major bleeding; and 4) net adverse clinical event (composite ischemia or non-CABG–related major bleeding) at 30 days. The definitions of clinical endpoints have been previously described (13). ST was classified according to the Academic

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Research Consortium criteria (17). We compared baseline characteristics and outcomes according to the presence of thrombus and assessed the independent impact of thrombus on 30-day and 1-year outcomes. Furthermore, we evaluated the effect of antithrombin therapy on composite ischemia or non-CABG–related bleeding in patients with thrombus. All endpoints were adjudicated by a clinical events committee blinded to the treatment assignment.

Continuous variables were compared using the Kruskal-Wallis test. Categorical values were compared by the chi-square or Fisher's exact test. For comparison of cumulative 30-day and 1-year outcomes between the 2 groups, we used Kaplan-Meier survival analysis and the log-rank test. Cox proportional hazard regression analysis was performed to determine the predictors of: 1) pre-procedural thrombus; and 2) individual components of composite ischemia, major bleeding, and ST. The following variables considered for the pre-procedural thrombus model included: age (per 10-year increment), sex, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, current smoking, previous MI, previous PCI, previous CABG, chronic renal insufficiency, baseline anemia, planned GPI use (bivalirudin or heparin plus a GPI) versus planned non-GPI use (bivalirudin monotherapy), aspirin or thienopyridine on admission or pre-procedure, duration from first study drug to angiogram, number of diseased vessels, extent of CAD (per 10-mm increment of lesions >30%), right CAD versus non–right CAD, reference vessel diameter, proximal lesion. Variable for the components of composite ischemia, major bleeding, and ST included: thrombus, age (per 10-year increment), sex, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, current smoking, previous MI, previous PCI, previous CABG, renal insufficiency, baseline anemia, baseline white blood cell count (per 1,000 increase), left ventricular ejection fraction (per 10% increase), biomarker elevation, ST-segment deviation, bivalirudin plus a GPI (vs. heparin plus a GPI), bivalirudin alone (vs. heparin plus a GPI), extent of CAD, number of diseased vessels, left anterior descending artery disease, proximal lesion, baseline TIMI flow grade, baseline blush score, eccentricity, ulceration, aneurysm, moderate-to-severe calcification, presence or absence of collaterals, worst percent diameter stenosis, stent type (drug-eluting stent [DES] vs. bare-metal stent [BMS]), use of ≥2 stents, aspiration device use, distal protection device use, aspirin at discharge, and thienopyridine at discharge.

To evaluate the relation between thrombus burden and ST, patients with measurable thrombus area (n = 432, 81.5%) were divided into tertiles of thrombus area (≤17 mm^2, n = 156; 17 to 32 mm^2, n = 135; and >32 mm^2, n = 141). All analyses were based on intention to treat. The p values, odds ratios (OR), and corresponding 2-sided 95% confidence intervals (CI) for predictors are presented.

Results

Baseline characteristics. Pre-procedural thrombus was present in 530 (15%) patients. Patients with thrombus were younger, were more frequently male, had lower prevalence of comorbidities including diabetes, hypertension, hyperlipidemia, and chronic renal insufficiency, and had less previous MI and PCI (Table 1). Current smoking, baseline troponin elevation, and ST-segment deviation was more common in patients with thrombus.

Study drug and procedural characteristics. The bail-out use of GPI in the bivalirudin monotherapy group was more frequent in patients with thrombus versus without thrombus (17.3% vs. 6.5%, p < 0.0001) (Table 2). BMS use was significantly higher in patients with thrombus than those without thrombus. Although thrombus aspiration or distal protection device were used more frequently in patients with thrombus, overall usage was low. Among patients with thrombus, those treated with versus without thrombus aspiration had similar rates of composite ischemia at 30 days (14.1% vs. 12.9%, p = 0.81) and at 1 year (22.7% vs. 21.8%, p = 0.72). Medication use after discharge was similar between the 2 groups, except for greater use of beta-blockers in the thrombus group (83.4% vs. 77.3%, p = 0.002).

Baseline and final angiographic characteristics. Left ventricular ejection fraction was lower in patients with thrombus than

Table 1. Baseline Clinical Characteristics

	Thrombus (+) (n = 530)	Thrombus (−) (n = 3,097)	p Value
Age, yrs	60 [52–69]	61 [53–71]	0.03
Male	73.6	69.0	0.04
Weight, kg	88 [77–100]	87 [75–100]	0.14
Diabetes	26.1	33.0	0.002
Insulin-treated diabetes	7.6	9.6	0.15
Hypertension	61.5	71.7	<0.0001
Hyperlipidemia	49.5	64.2	<0.0001
Current smoker	40.2	30.0	<0.0001
Previous MI	30.5	35.3	0.03
Previous PCI	31.6	50.9	<0.0001
Previous CABG	19.7	22.4	0.17
Renal insufficiency*	13.5	17.6	0.02
Baseline cardiac biomarker elevation or ST-segment deviation	86.6	62.9	<0.0001
Baseline troponin elevation	79.8	52.4	<0.0001
ST-segment deviation ≥1 mm	30.0	25.1	0.02
TIMI risk score			
0–2	16.1	12.4	0.04
3–4	56.5	55.7	0.80
5–7	27.5	31.8	0.07

Values are median [interquartile range] or %. *Renal insufficiency was defined as calculated creatinine clearance <60 ml/min by the Cockcroft-Gault equation.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

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Table 2. Drug and Procedural Characteristics

	Thrombus (+) (n = 530)	Thrombus (−) (n = 3,097)	p Value
Antithrombin assignment			
Heparin (UFH or LMWH) plus a GPI	30.8	32.8	0.37
Upstream GPI use	16.8	15.9	0.61
Deferred GPI use	14.0	16.9	0.10
Bivalirudin plus a GPI	32.1	34.6	0.28
Upstream GPI use	19.1	17.5	0.39
Deferred GPI use	13.0	17.1	0.02
Bivalirudin monotherapy	37.2	32.6	0.04
Bail-out use of GPI	17.3	6.5	<0.0001
Duration from first study drug to angiography, h	2.8 [0.9–12.5]	2.9 [0.9–13.5]	0.51
Duration from first study drug to PCI, h	3.4 [1.3–13.8]	3.4 [1.3–15.0]	0.67
PCI procedure			
Stent use	93.8	93.7	0.99
DES	81.5	85.1	0.04
BMS	20.4	14.6	0.0009
Both	8.1	6.0	0.07
Thrombus aspiration	9.4	1.2	<0.0001
Distal protection devices	4.2	1.7	0.0007
Medications after discharge			
Aspirin	97.0	97.0	1.00
Thienopyridines	94.9	94.0	0.18
Statins	85.0	83.2	0.33
Beta-blocker	83.4	77.3	0.002
ACE inhibitor	57.5	56.6	0.73

Values are median [interquartile range] or %.

ACE = angiotensin-converting enzyme; BMS = bare-metal stent(s); DES = drug-eluting stent(s); GPI = glycoprotein IIb/IIIa inhibitor; LMWH = low molecular-weight heparin; UFH = unfractionated heparin; other abbreviations as in Table 1.

those without thrombus (Table 3). Patients with thrombus had more frequent right coronary artery target lesions, proximal coronary location, larger vessels, and more severe diameter stenosis compared with patients without thrombus. Patients with thrombotic lesions had more TIMI flow grade 0/1 at baseline and had lower rates of TIMI flow grade 3 and myocardial blush grade 3 after final intervention despite having better acute luminal results with larger minimum lumen diameter than patients without thrombus. Procedural complications such as spasm, abrupt closure, distal embolism, or no-reflow were all more frequent in patients with thrombus (Table 3).

Predictor of pre-procedural thrombus formation. After adjusting demographic, treatment, and angiographic covariates, predictors of pre-procedural thrombus formation included baseline reference diameter (OR: 1.67 [95% CI: 1.40 to 1.98], $p < 0.0001$), Jeopardy Score (OR: 1.14 [95% CI: 1.09 to 1.18], $p < 0.0001$), current smoking (OR: 1.31 [95% CI: 1.07 to 1.60], $p = 0.01$), and right CAD (OR: 1.43 [95% CI: 1.09 to 1.88], $p = 0.01$). By contrast, the following factors were protective of pre-procedural thrombus formation: previous PCI (OR: 0.60 [95% CI: 0.47 to 0.75], $p < 0.0001$), hyperlipidemia (OR: 0.74 [95% CI: 0.60 to 0.92], $p = 0.006$), triple-vessel disease (OR: 0.74 [95% CI: 0.59 to 0.93], $p = 0.01$), planned GPI use (OR: 0.80 [95% CI: 0.65 to 0.98], $p = 0.03$), and thienopyridines on admission (OR: 0.77 [95% CI: 0.59 to 0.99], $p = 0.04$).

Table 3. Baseline and Final Angiographic Characteristics

	Thrombus (+) (n = 530)	Thrombus (−) (n = 3,097)	p Value
Left ventricular ejection fraction, %	62 [55–70]	66 [57–73]	<0.0001
Culprit lesion location			
LAD	32.2	42.9	<0.0001
RCA	46.4	38.0	0.0004
LCX	36.9	36.9	1.00
Number of diseased lesions	4.3 ± 2.7	4.3 ± 2.6	0.57
Number of attempted vessels	1.2 ± 0.4	1.2 ± 0.4	0.19
Proximal lesion	44.0	36.3	0.0001
TIMI flow grade			
Baseline			
0/1	47.5	17.6	<0.0001
2	16.7	13.0	0.03
3	35.8	69.4	<0.0001
Final			
0/1	5.3	1.2	<0.0001
2	5.1	1.7	<0.0001
3	89.6	97.1	<0.0001
Blush score			
Baseline			
0/1	49.4	17.8	<0.0001
2	13.7	19.4	0.002
3	36.9	62.8	<0.0001
Final			
0/1	6.6	2.0	<0.0001
2	15.0	11.5	0.03
3	78.4	86.7	<0.0001
Reference diameter, mm			
Baseline	2.9 ± 0.6	2.7 ± 0.6	<0.0001
Final	3.0 ± 0.6	2.8 ± 0.6	<0.0001
Minimum lumen diameter, mm			
Baseline	0.5 ± 0.5	0.8 ± 0.5	<0.0001
Final	2.4 ± 0.7	2.3 ± 0.6	0.0009
Diameter stenosis, %			
Baseline	83.8 ± 16.4	71.9 ± 15.1	<0.0001
Final	19.1 ± 15.8	16.8 ± 10.7	0.0003
Periprocedural complications			
Spasm	4.7	2.4	0.003
Abrupt closure	2.8	0.4	<0.0001
Distal embolization	4.2	0.2	<0.0001
No reflow	1.3	0.4	0.01
Perforation	0.2	0.2	1.00

Values are median [interquartile range] %, or mean ± SD.

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; other abbreviations as in Table 1.

Association of thrombus with clinical outcomes. At 30 days, patients with thrombus had a worse net adverse clinical event (18.3% vs. 14.0%, p = 0.006) and composite ischemia (13.0% vs. 9.4%, p = 0.007) with a higher incidence of death (1.5% vs. 0.7%, p < 0.05) and MI (10.6% vs. 7.1%, p = 0.004) versus those without thrombus (Table 4). Unplanned revascularization and bleeding rate were similar in the 2 groups at 30 days. At 1 year, composite ischemia was similar between the 2 groups (21.9% vs. 20.7%, p = 0.52); however, the higher incidence of MI in the thrombus group persisted at 1 year (14.3% vs. 9.9%, p = 0.002) (Table 4). A landmark analysis (Figs. 1A to 1D) demonstrated that the higher event rates associated with the presence of thrombus was due to early events up to 30 days, including higher death and MI. Conversely, from 30 days to 1 year, composite ischemia was lower in patients with thrombus, due to a lower mortality (relative risk [RR]: 0.35 [95% CI: 0.13 to 0.97], p = 0.03) and lower rate of unplanned revascularization (RR: 0.63 [95% CI: 0.44 to 0.91], p = 0.01).

In multivariable analysis, pre-procedural thrombus was an independent predictor of 30 day death (OR: 3.16 [95% CI: 1.20 to 8.37], p = 0.02) and MI (OR: 1.62 [95% CI: 1.17 to 2.24], p = 0.003) and cumulative MI at 1 year (OR: 1.56 [95% CI: 1.16 to 2.08], p = 0.003). However, the presence of thrombus did not predict ischemic events between 30 days to 1 year (death: OR: 0.32 [95% CI: 0.10 to 1.04], p = 0.06, MI: OR: 1.34 [95% CI: 0.77 to 2.33], p = 0.30, or unplanned revascularization: OR: 0.85 [95% CI: 0.52 to 1.40], p = 0.53]).

Association of thrombus with ST. Cumulative ST at 1 year was higher in patients with thrombus, mainly due to the higher rates at 30 days (Fig. 1E, Table 4). By multivariable analysis, pre-procedural thrombus was an independent predictor of ST at 30 days (OR: 2.61 [95% CI: 1.38 to 4.92], p = 0.003) and cumulatively at 1 year (OR: 2.98 [95% CI: 1.64 to 5.42], p = 0.0003), but did not predict ST between 30 days to 1 year (OR: 1.38 [95% CI: 0.39 to 4.88], p = 0.62). We found no association between thrombus burden and ST at 30 days (first tertiles: 1.9% vs. second tertiles: 3.7% vs. third tertiles: 2.1%, p = 0.58) and at 1 year (3.6% vs. 3.7% vs. 2.9%, p = 0.92). Patients with thrombus treated with BMS (n = 98) versus DES (n = 432) had no significant differences in rates of ST at 30 days (1.0% vs. 3.3%, p = 0.23) and at 1 year (4.1% vs. 2.1%, p = 0.36), although the numbers were small.

Effects of antithrombotic regimens on clinical outcomes in patients with thrombus. Among the 530 patients with thrombus, antithrombotic treatment allocation included heparin plus a GPI (n = 163), bivalirudin plus a GPI (n = 170), or bivalirudin alone (n = 197). Major bleeding at 30 days was reduced by 60% with bivalirudin alone compared with heparin plus a GPI (Table 5). There was no difference in 30-day and 1-year net adverse clinical events or composite ischemia among antithrombin groups (Table 5). The use of bail-out GPI in the bivalirudin monotherapy group did not affect composite ischemia at 30 days (11.8% vs. 16.6%, p = 0.48) or at 1 year (20.7% vs. 19.7%, p = 0.90). Among the 170 patients with thrombus receiving bivalirudin plus a GPI, the assignment to upstream versus deferred GPI therapy resulted in a significant reduction in 1-year composite ischemia (13.1% vs. 27.4%, p = 0.03) and MI (9.0% vs. 21.2%, p = 0.03) (Table 6).

Discussion

Thrombotic lesions remain a common finding in patients with moderate- and high-risk ACS undergoing early an-

Table 4. Clinical Outcomes

Outcomes, %	Thrombus (+) (n = 530)	Thrombus (−) (n = 3,097)	p Value	Adjusted OR [95% CI]	Adjusted p Value
30 days					
Net adverse clinical event	18.3	14.0	0.006	1.29 [0.99–1.70]	0.06
Composite ischemia	13.0	9.4	0.007	1.49 [1.10–2.01]	0.009
Death	1.5	0.7	<0.05	3.16 [1.20–8.37]	0.02
MI	10.6	7.1	0.004	1.62 [1.17–2.24]	0.003
Unplanned revascularization	4.2	3.5	0.42	1.20 [0.75–1.92]	0.45
Major bleeding	7.2	6.1	0.32	1.30 [0.87–1.94]	0.20
Stent thrombosis*	2.8	1.1	0.002	2.61 [1.38–4.92]	0.003
1 year					
Composite ischemia	21.9	20.7	0.52	1.30 [0.98–1.72]	0.07
Death	2.3	3.0	0.48	0.94 [0.45–1.97]	0.87
MI	14.3	9.9	0.002	1.56 [1.16–2.08]	0.003
Unplanned revascularization	11.3	13.7	0.10	1.24 [0.87–1.77]	0.23
Stent thrombosis*	3.7	1.8	0.003	2.98 [1.64–5.42]	0.0003

*Definite/probable stent thrombosis according to Academic Research Consortium (ARC) definitions.
CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

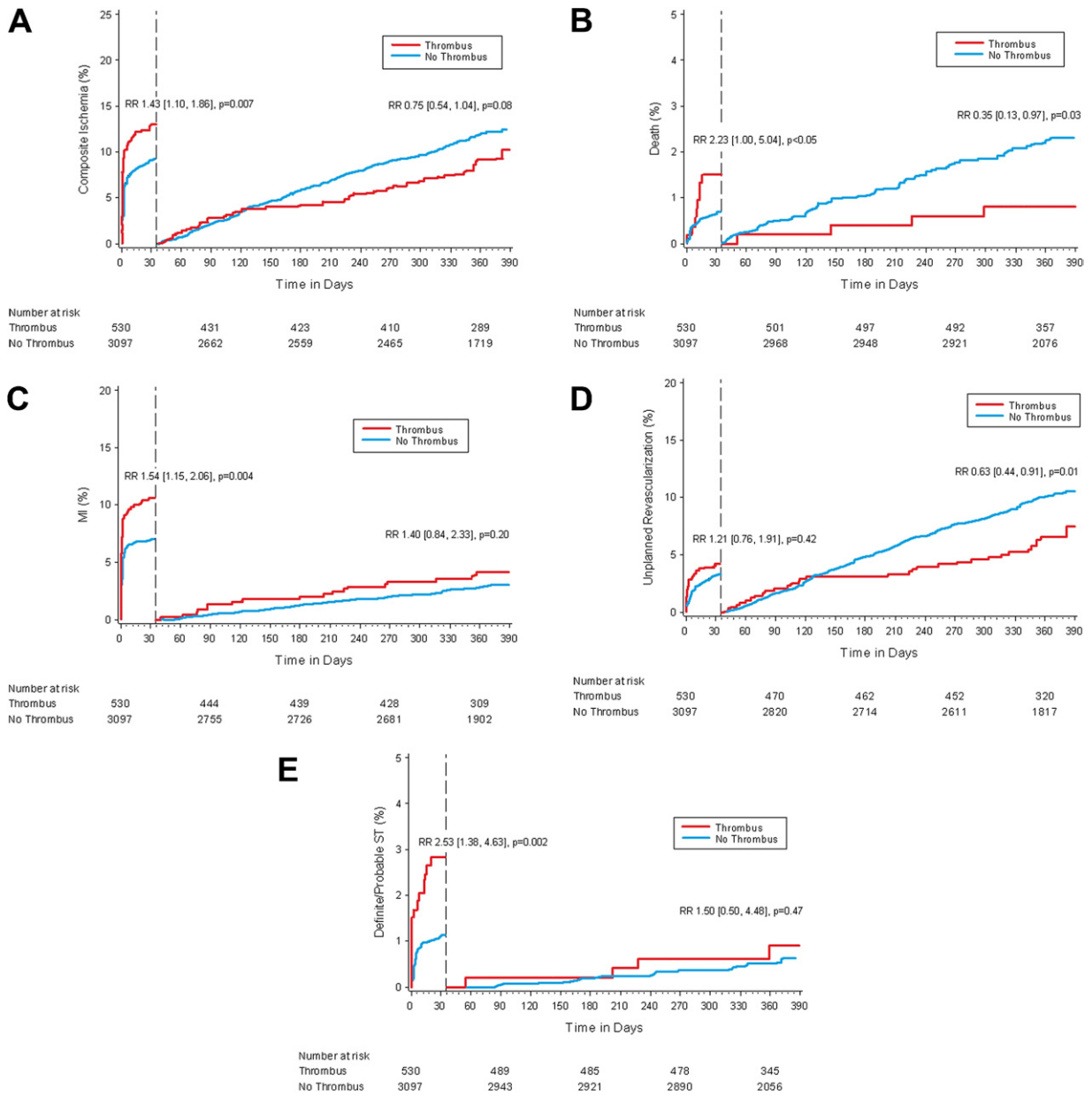

Figure 1. Landmark Analyses

Landmark analyses of **(A)** composite ischemia, **(B)** death, **(C)** MI, **(D)** unplanned revascularization, and **(E)** definite or probable ST up to 30 days and from 30 days to 1 year in patients with versus without thrombus. MI = myocardial infarction; RR = relative risk; ST = stent thrombosis.

giography and triage to PCI. The presence of thrombus increases procedural complications, likely explaining the associated ischemic complications. Baseline lesion thrombus predicted 30-day mortality, MI, and ST, as well as cumulative MI and ST 1 year following PCI, with more than a 2-fold increased risk of death or ST and 1.5 times risk of MI at 30 days. Paradoxically, baseline thrombus identifies a population with lower risk of mortality and need for unplanned revascularization between 30 days to 1 year. Planned GPI and thienopyridine use on admission predicted less thrombus, but the antithrombotic regimen did not affect ischemic outcomes of patients with thrombus. Bivalirudin monotherapy reduced bleeding complications, and for those patients with thrombus, upstream use of GPI (vs. deferred GPI) on a background of bivalirudin monotherapy reduced 1-year composite ischemia and MI.

Prevalence of thrombus on baseline angiography. Previous studies have reported an incidence of thrombus ranging from

Table 5. Clinical Outcomes at 30 Days and at 1 Year in Patients With Thrombus

	Heparin (UFH or LMWH) + GPI (n = 163)	Bivalirudin + GPI (n = 170)	Bivalirudin Monotherapy (n = 197)	p Value*	p Value†	p Value‡
At 30 days, %						
Net adverse clinical event	22.2	17.7	15.7	0.34	0.12	0.60
Composite ischemia	15.4	10.0	13.7	0.16	0.69	0.29
Death	3.1	0.6	1.0	0.09	0.15	0.66
Nonfatal MI	10.5	8.9	12.2	0.62	0.61	0.30
Unplanned revascularization	5.0	3.0	4.6	0.36	0.86	0.43
Major bleeding	10.5	8.3	3.6	0.51	0.009	0.05
Stent thrombosis	3.1	2.4	3.1	0.69	0.97	0.69
At 1 year, %						
Composite ischemia, %	27.4	18.9	19.9	0.14	0.23	0.77
Death	4.4	1.2	1.5	0.08	0.10	0.78
Nonfatal MI	13.2	14.0	15.5	0.94	0.56	0.63
Unplanned revascularization	16.2	8.7	9.7	0.12	0.21	0.75
Stent thrombosis	3.1	4.2	3.8	0.64	0.82	0.78

†Comparison between heparin (UFH or LMWH) + GPI versus bivalirudin + GPI. ‡Comparison between heparin (UFH or LMWH) + GPI versus bivalirudin alone. §Comparison between bivalirudin + GPI versus bivalirudin alone.
Abbreviations as in Tables 1 and 2.

7% to 23% in patients with unstable angina (1,18–20), depending on disease acuity, epicardial blood flow, cardiac marker elevation, and the timing of angiography (1,7,18,21). Consistent with prior studies, larger vessel diameter, right CAD, higher Jeopardy Score, and active smoking history predicted thrombotic lesions (21,22). In addition, the planned use of GPI (non-bail out) was associated with a 20% lower frequency of pre-procedural lesion thrombus (OR: 0.80 [95% CI: 0.65 to 0.98], p = 0.03), consistent with findings in the PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) and CAPTURE trials with prolonged 18 to 48 h of GPI + heparin therapy (22,23). Shorter 90-min infusions of intravenous GPI have also shown benefit in reducing thrombus (21), and our study shows that the benefits of planned GPI can be seen with shorter infusions yet, with the median time from first study drug to PCI in ACUITY being 2.9 h (9,10). Although planned GPI use reduced the occurrence of thrombus, there was no significant difference noted in ischemic outcomes from any of the 3 antithrombotic regimens tested (24).

Table 6. Clinical Outcomes at 30 Days and at 1 Year in Patients With Thrombus Assigned to Bivalirudin Plus a GPI

	Upstream GPI (n = 101)	Deferred GPI (n = 69)	p Value
At 30 days, %			
Net adverse clinical event	13.9	23.3	0.12
Composite ischemia	6.9	14.5	0.10
Death	0	1.4	0.22
MI	5.9	13.2	0.11
Unplanned revascularization	3.0	2.9	0.98
Major bleeding	6.9	10.3	0.44
Stent thrombosis	2.0	2.9	0.70
At 1 year, %			
Composite ischemia	13.1	27.4	0.03
Death	1.0	1.4	0.78
MI	9.0	21.2	0.03
Unplanned revascularization	7.1	10.7	0.47
Stent thrombosis	4.0	4.4	0.91

Abbreviations as in Tables 1 and 2.

Treatment and procedural results. Consistent with previous studies, procedural failure and complications, including abrupt closure, distal embolism, reduced epicardial and myocardial perfusions, and slow flow remained higher in patients with thrombus even after the introduction of a stent or GPI (1,7), and likely contribute to the increased 30-day ischemic complications (25) and mortality (21,22,26–28). The landmark analysis demonstrated that the negative clinical impact of thrombotic lesions appears to be limited to the first 30 days, during which patients with thrombus had significantly higher composite ischemia following PCI, with a 3-fold increase in mortality and a 1.5-fold increase in MI rate. Additional pharmacological interventions and/or mechanical devices should be studied to prevent or treat intracoronary thrombus.

Pre-procedural thrombus and clinical outcome. The presence of baseline thrombus worsens the clinical presentation of patients with more frequent troponin elevation (1,18), but paradoxically, was comprised of a lower-risk population characterized by younger age, less diabetes, hypertension, hyperlipidemia, renal insufficiency, and history of prior MI or PCI than patients without thrombus, which likely explains the lower event rate seen in the landmark analysis between 30 days and 1 year. Nevertheless, after adjusting for

all differences in demographics, angiographic characteristics, and PCI procedures, thrombus remained independently predictive of mortality, MI, and ST at 30 days as well as cumulative rates of MI and ST at 1 year.

The presence of thrombus has been clearly identified as a factor predisposing to ST (23,29), and in ACUITY, we show a more than 2-fold increase in acute and subacute ST despite contemporary PCI, optimal GPI, and antiplatelet therapy, but no relationship with thrombus burden in contrast to a prior report (7). Beyond 30 days, there was no apparent added risk of late ST as a result of the initial thrombotic lesion. The absence of persistent risk beyond 30 days would suggest that this population is not at long-term systemic thrombotic risk but rather subject to an acute thrombogenic mechanism likely localized to a ruptured plaque. Considering the significant early ischemic risk, patients with thrombotic lesions on initial angiography may well benefit from optimal antiplatelet pre-loading and may justify the use of more potent thienopyridines (30).

Effects of antithrombotic treatments on outcomes in patients with thrombus. The selection of the antithrombotic regimen (heparin plus a GPI vs. bivalirudin plus a GPI vs. bivalirudin monotherapy) did not impact subsequent ischemic events among patients with thrombus. Although bivalirudin monotherapy reduced bleeding complications, the planned upstream use of GPI did appear to have a role in reducing both the frequency of thrombus formation, as well as ischemic complications in thrombotic patients. These benefits were offset by higher bleeding consequences at the systemic GPI doses tested. Whether localized intracoronary dosing of GPI may afford ischemic benefit for thrombotic patients without raising the bleeding risk remains to be evaluated.

Study limitations. This study is a retrospective analysis, and is therefore hypothesis generating. The study results only apply to the specific population evaluated. The incidence of thrombus in the study is likely underestimated due to the imperfect sensitivity of angiography in detecting thrombus (2), and thrombus burden modification related to pre-procedural pharmacotherapy cannot be excluded (18). Further, the evaluation of antithrombotic regime on clinical outcomes is a subset analysis of this subgroup and is entirely hypothesis generating, but provides insight into possible pharmacological alternatives to prevent or treat intra-coronary thrombus.

Conclusions

Pre-procedural thrombus remains common (15%) among moderate- and high-risk ACS patients undergoing contemporary PCI. Baseline thrombus predicted 30-day ischemic complications, including a 3-fold increased mortality risk. Beyond 30 days, ischemic and mortality complications were reduced, suggesting absence of persistent thrombotic risk. Further evaluation of adjunctive pharmacology is needed to reduce ischemic complications in this high-risk population.

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REFERENCES

1. Singh M, Berger PB, Ting HH, et al. Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era (the Mayo Clinic experience). Am J Cardiol 2001;88:1091–6.
2. White CJ, Ramee SR, Collins TJ, et al. Coronary thrombi increase PTCA risk. Angioscopy as a clinical tool. Circulation 1996;93:253–8.
3. de Feyter PJ, de Jaegere PPT, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994;127:643–51.
4. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
5. Javaid A, Siddiqi NH, Steinberg DH, et al. Adjunct thrombus aspiration reduces mortality in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction with high-risk angiographic characteristics. Am J Cardiol 2008;101:452–56.
6. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet 2008;371:1915–20.
7. Sianos G, Papafaklis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol 2007;50:573–83.
8. Hong MK, Mintz GS, Lee CW, et al. Incidence, mechanism, predictors, and long-term prognosis of late stent malapposition after bare-metal stent implantation. Circulation 2004;109:881–6.
9. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol 2007;50:e1–157.
10. Bassand JP, Hamm CW, Ardissino D, et al., Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598–660.
11. White HD, Ohman EM, Lincoff AM, et al. Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol 2008;52:807–14.
12. Stone GW, McLaurin BT, Cox DA, et al., for the ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203–16.
13. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial: study design and rationale. Am Heart J 2004;148:764–75.
14. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase findings. N Engl J Med 1985;312:932–6.
15. van't Hof AW, Liem A, Suryapranata H, et al., for the Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302–6.
16. Califf RM, Phillips HR 3rd, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985;5:1055–63.
17. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
18. Heeschen C, van Den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. Circulation 1999;100:1509–14.

19. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L, for the FRISC II (Fast Revascularization during InStability in CAD) Investigators. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. J Am Coll Cardiol 2001;38:979–86.
20. Jurlander B, Farhi ER, Banas JJ Jr., et al. Coronary angiographic findings and troponin T in patients with unstable angina pectoris. Am J Cardiol 2000;85:810–4.
21. Gibson CM, de Lemos JA, Murphy SA, et al., for the TIMI Study Group. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. Circulation 2001;103:2550–4.
22. Zhao XQ, Theroux P, Snapinn SM, et al., for the PRISM-PLUS Investigators. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non–Q-wave myocardial infarction. Angiographic results from the PRISM-PLUS trial (platelet receptor inhibition for ischemic syndrome management in patients limited by unstable signs and symptoms). Circulation 1999;100:1609–15.
23. Uren NG, Schwarzacher SP, Metz JA, et al., for the POST Registry Investigators. Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. Eur Heart J 2002;23:124–32.
24. Stone GW, Bertrand ME, Moses JW, et al., for the ACUITY Investigators. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA 2007;297:591–602.
25. Stone GW, Webb J, Cox DA, et al., for the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) Investigators. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063–72.
26. Simes RJ, Topol EJ, Holmes DR, et al., for the GUSTO-I Investigators. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. Circulation 1995;91:1923–8.
27. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am Coll Cardiol 2002; 39:591–7.
28. Freeman MR, Williams AE, Chisholm RJ, Armstrong PW. Intracoronary thrombus and complex morphology in unstable angina. Relation to timing of angiography and in-hospital cardiac events. Circulation 1989;80:17–23.
29. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;108:43–7.
30. Montalescot G, Wiviott SD, Braunwald E, et al., for the TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.
31. Stone GW, White HD, Ohman EM, et al., for the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial Investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet 2007;369:907–19.

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